REMARKS

Claims 1-52 were pending in the present application. Claims 53-68 are added, Claims 5-7, 17-19, 33-35, and 45-47 are cancelled, and Claims 1, 2, 4, 13, 14, 16, 29, 30, 32, 41, 42, and 44 are amended in the present amendment. Accordingly, Claims 1-4, 8-16, 20-32, 36-44, and 48-68 are pending and under consideration in the present application following entry of the present amendment.

Applicants note with appreciation the withdrawal of the restriction requirement mailed April 24, 2002, and kindly thank the PTO for the same.

I. Amendments to the Specification

The specification has been amended to incorporate by reference and to claim the benefit of U.S. provisional application No. 60/198,336 in the first sentence of the application and to explicitly describe subject matter previously incorporated by reference. The amendments to the specification are fully supported by the disclosure of the application as filed.

The New Application Transmittal filed together with the present application on April 18, 2000, claims the benefit, under 35 U.S.C. § 119(e), of U.S. provisional application No. 60/198,336 at page 2, approximate lines 15-16. Accordingly, the amendment to the specification claiming such priority does not constitute new matter.

With regard to the other amendment, the specification is amended to clarify that use of thermostable DNA polymerase enzymes that naturally comprise the critical motif is also within the scope of the invention. This amendment is supported by the disclosure of co-pending U.S. Application No. 09/146,631, which disclosure is incorporated by reference into the specification of the present application at page 3, lines 24-27. U.S. Application No. 09/146,631 has since issued as U.S. Patent No. 6,346,379 ("the '379 patent").

At column 17, lines 28-39, the '379 patent describes a thermostable DNA polymerase that comprises a critical motif that is not derived by mutation. At page 3, lines 17-23, the present specification describes use of the thermostable DNA polymerases described in the '379 patent in the methods of the present application. Thus, the specification describes the use of thermostable DNA polymerases that naturally comprise the critical motif in the methods of the present invention. The amended paragraph of the instant specification differs from that of the '379 patent only in that the amendment to the instant specification refers to the methods of the present invention rather than those described and claimed in the '379 patent. Applicants note that the present application and the '379 patent both describe

methods of using DNA polymerases that comprise a critical motif, albeit for different purposes as discussed in detail below.

Accordingly, the amendment to the specification does not present new matter. Entry of the amendment to the specification under 37 C.F.R. § 1.111 is therefore respectfully requested.

II. Amendments to the Claims

The claims have been amended without prejudice in order to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention and to add limitations which had been mistakenly omitted from the claims, but not the specification. Specifically, Claims 53-68 are added, Claims 5-7, 17-19, 33-35, and 45-47 are cancelled, and Claims 1, 2, 4, 13, 14, 16, 29, 30, 32, 41, 42, and 44 are amended in the present amendment. The amendments do not introduce new matter and are fully supported by the specification and claims of the present application as originally filed.

In particular, Claims 1, 13, 29, and 41 have been amended to correspond to a method of using the amino acid sequence of the critical motif (SEQ ID NO:1) of the described thermostable DNA polymerases. Support for the amendments to Claims 1, 13, 29, and 41 may be found, for example, in the specification at page 4, lines 17-22, and in Claims 1, 13, 29, and 41 as originally filed.

Similarly, Claims 2, 14, 30, and 42 have been amended to correspond to a method of using the amino acid sequence of the critical motif (SEQ ID NO:2) of the described thermostable DNA polymerases. Support for the amendments to Claims 2, 14, 30, and 42 may be found, for example, in the specification at page 4, lines 23-27 and in Claims 2, 14, 30, and 42 as originally filed.

Likewise, Claims 4, 16, 32, and 44 have been amended to correspond to a method of using the amino acid sequence of the critical motif (SEQ ID NO:4) of the described thermostable DNA polymerases. Support for the amendments to Claims 4, 16, 32, and 44 may be found, for example, in the specification at page 5, lines 3-7 and in Claims 4, 16, 32, and 44 as originally filed.

Applicants respectfully submit that the limitations added to the amended claims were inadvertently omitted from the claims as filed and have been re-introduced merely to expedite prosecution. Applicants maintain that the amended claims are fully patentable as filed and do not assert that the patentability of the present claims depends on the limitations added by the present amendment.

New Claims 53-68 have been added in order to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. New Claims 53-68 are fully supported by the specification and claims of the present application as filed and do not introduce any new matter.

New Claim 53 recites a method of reverse transcribing an RNA that comprises, among other elements, providing a thermoactive DNA polymerase characterized in that in its native form, the polymerase comprises SEQ ID NO:1, wherein the amino acid at position 4 is other than E, A, G, or P, the amino acid at position 2 is S or A, and the amino acid at position 5 is L or I. Support for new Claim 53 may be found, for example, in the paragraph of the specification added by the present amendment, at page 4, lines 17-22, and in Claim 1 as originally filed.

New Claim 54 depends from new Claim 53 and further defines the amino acid sequence recited in Claim 53 as the amino acid sequence of SEQ ID NO:5, wherein the amino acid at position 7 is V or I. Support for new Claim 54 may be found, for example, at page 5, lines 8-12, and in Claim 5 as originally filed. New Claim 55 also depends from new Claim 53 and further defines the amino acid sequence recited in Claim 53 as the amino acid sequence of SEQ ID NO:6. Support for new Claim 55 may be found, for example, at page 5, lines 13-17, and in Claim 6 as originally filed. New Claim 56 also depends from new Claim 53 and further defines the amino acid sequence recited in Claim 53 as the amino acid sequence of SEQ ID NO:7, wherein the amino acid at position 8 is S or T. Support for new Claim 56 may be found, for example, at page 5, lines 18-21, and in Claim 7 as originally filed.

New Claim 57 recites a method for reverse transcribing an RNA that comprises, among other elements, providing a thermoactive DNA polymerase characterized in that in its native form, the polymerase comprises SEQ ID NO:1, wherein the amino acid at position 4 is other than E, A, G, or P, the amino acid at position 2 is S or A, and the amino acid at position 5 is L or I. Support for new Claim 57 may be found, for example, in the paragraph of the specification added by the present amendment, at page 4, lines 17-22, and in Claim 13 as originally filed.

New Claim 58 depends from new Claim 57 and further defines the amino acid sequence recited in Claim 57 as the amino acid sequence of SEQ ID NO:5, wherein the amino acid at position 7 is V or I. Support for new Claim 58 may be found, for example, at page 5, lines 8-12, and in Claim 14 as originally filed. New Claim 59 also depends from new Claim 57 and further defines the amino acid sequence recited in Claim 57 as the amino acid

sequence of SEQ ID NO:6. Support for new Claim 59 may be found, for example, at page 5, lines 13-17, and in Claim 15 as originally filed. New Claim 60 also depends from new Claim 57 and further defines the amino acid sequence recited in Claim 57 as the amino acid sequence of SEQ ID NO:7, wherein the amino acid at position 8 is S or T. Support for new Claim 60 may be found, for example, at page 5, lines 18-21, and in Claim 16 as originally filed.

New Claim 61 recites a method for amplifying an RNA using a single-enzyme reverse-transcription/amplification reaction that comprises, among other elements, providing a thermoactive DNA polymerase characterized in that in its native form, the polymerase comprises SEQ ID NO:1, wherein the amino acid at position 4 is other than E, A, G, or P, the amino acid at position 2 is S or A, and the amino acid at position 5 is L or I. Support for new Claim 61 may be found, for example, in the paragraph of the specification added by the present amendment, at page 4, lines 14-22, and in Claim 29 as originally filed.

New Claim 62 depends from new Claim 61 and further defines the amino acid sequence recited in Claim 61 as the amino acid sequence of SEQ ID NO:5, wherein the amino acid at position 7 is V or I. Support for new Claim 62 may be found, for example, at page 5, lines 8-12, and in Claim 33 as originally filed. New Claim 63 also depends from new Claim 61 and further defines the amino acid sequence recited in Claim 61 as the amino acid sequence of SEQ ID NO:6. Support for new Claim 63 may be found, for example, at page 5, lines 13-17, and in Claim 34 as originally filed. New Claim 64 also depends from new Claim 61 and further defines the amino acid sequence recited in Claim 61 as the amino acid sequence of SEQ ID NO:7, wherein the amino acid at position 8 is S or T. Support for new Claim 64 may be found, for example, at page 5, lines 18-21, and in Claim 35 as originally filed.

New Claim 65 recites a method for amplifying an RNA using a single-enzyme reverse-transcription/amplification reaction that comprises, among other elements, providing a thermoactive DNA polymerase characterized in that in its native form, the polymerase comprises SEQ ID NO:1, wherein the amino acid at position 4 is other than E, A, G, or P, the amino acid at position 2 is S or A, and the amino acid at position 5 is L or I. Support for new Claim 65 may be found, for example, in the paragraph of the specification added by the present amendment, at page 4, lines 17-22, and in Claim 41 as originally filed.

New Claim 66 depends from new Claim 65 and further defines the amino acid sequence recited in Claim 65 as the amino acid sequence of SEQ ID NO:5, wherein the amino acid at position 7 is V or I. Support for new Claim 66 may be found, for example, at

page 5, lines 8-12, and in Claim 45 as originally filed. New Claim 67 also depends from new Claim 65 and further defines the amino acid sequence recited in Claim 65 as the amino acid sequence of SEQ ID NO:6. Support for new Claim 66 may be found, for example, at page 5, lines 13-17, and in Claim 46 as originally filed. New Claim 68 also depends from new Claim 65 and further defines the amino acid sequence recited in Claim 65 as the amino acid sequence of SEQ ID NO:7, wherein the amino acid at position 8 is S or T. Support for new Claim 68 may be found, for example, at page 5, lines 18-21 and in Claim 47 as originally filed.

Applicants respectfully submit that the foregoing discussion of the amendments to the claims shows that the amendments are fully supported by the specification and claims as filed and thus do not present new matter. Accordingly, Applicants hereby respectfully request entry of the present amendment to the claims under 37 C.F.R. § 1.111.

III. Priority

The PTO has objected to the claim of priority to U.S. Provisional Application No. 60/198,336 on the grounds that the first sentence of the specification or an application data sheet does not contain a specific reference to the provisional application. The present amendment adds a claim of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 60/198,336 to the first sentence of the specification. Therefore, the present application fully complies with 35 U.S.C. § 119(e) and is entitled to the priority date of U.S. Provisional Application No. 60/198,336, filed April 18, 2000. Accordingly, Applicants respectfully request that the objection to the claim of priority to U.S. Provisional Application No. 60/198,336 be withdrawn.

IV. The Rejections

A. The Rejection of Claims 1, 8-13, 20-29, 36-41, and 48-52 under 35 U.S.C. § 112, First Paragraph

Claims 1, 8-13, 20-29, 36-41, and 48-52 stand rejected under 35 U.S.C. § 112, First Paragraph, as allegedly not enabled by the specification. In particular, the PTO asserts that the specification does not allow one of skill in the art to make and use every polymerase that comprises SEQ ID NO:1. Thus, the PTO alleges that the specification does not enable one of skill in the art to make or use the invention commensurate in scope with the rejected claims.

Applicants respectfully submit that Claims 1, 8-13, 20-29, 36-41, and 48-52, both as filed and as amended, are fully enabled by the specification of the present application.

Applicants have described a genus of DNA polymerase enzymes that can be used to reverse transcribe an RNA according to the claimed methods of the invention. One of only ordinary skill in the art can easily recognize and use *any* species within the genus of thermostable DNA polymerase enzymes recited by the claims. Accordingly, the present application fully enables the ordinarily skilled artisan to recognize and use the entire genus of thermostable DNA polymerase enzymes in the claimed methods with no more than routine experimentation.

1. ***The Legal Standard***

To satisfy 35 U.S.C. § 112, a specification must describe a claimed invention sufficiently to enable one of ordinary skill in the art to practice the invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The multi-factor test summarized by the Federal Circuit in *Wands* forms the basis for an inquiry into whether an amount of experimentation is undue.

The *Wands* factors include (1) the quantity of experimentation necessary, (2) the amount of guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5), the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *See id.* The test for determining whether experimentation is undue is "not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or the specification provides a reasonable amount of guidance with respect to ... the experimentation." *See Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982).

Finally, the PTO must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. "When rejecting a claim under the enablement requirement of § 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application..." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The PTO's *prima facie* case should address each of the *Wands* factors since "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others." *See* MPEP § 2164.01(a), citing *Wands* at 1407. Where the PTO does not provide evidence regarding one or more *Wands* factors, Applicants presume that such factors support the conclusion that the claims at issue are fully enabled.

2. ***Any Experimentation Required to Practice the Full Scope of the Invention as Claimed is Routine Rather than Undue***

Applicants respectfully submit that the nature of the present invention suggests that if any experimentation is required to practice the full scope of the claimed invention, it is merely routine. The invention relates to use of a genus of thermostable DNA polymerase enzymes to reverse transcribe an RNA. The genus of thermostable DNA polymerase enzymes useful in the methods of the invention is described to be those thermostable DNA polymerase enzymes which comprise a critical motif. As amended in the present application, the critical motif is LXXXXXXXXXXE, wherein X at position 2 is S or A, X at position 5 is L or I, and X at position 4 is other than E, A, G, or P.

One of ordinary skill in the art can, based on the disclosure of the application and the art as a whole, first routinely identify that an enzyme is a thermostable DNA polymerase based upon its functional and structural properties. The functional properties of thermostable DNA polymerases are well-known, and include, for example, thermostability and DNA polymerization activity. One of merely ordinary skill in the art can easily identify whether a particular enzyme is thermostable or has DNA polymerization activity by reference to the literature or with simple experiments well-known to the art. For example, the ordinarily-skilled artisan could identify that an enzyme has DNA polymerization activity by performing a primer extension assay. The thermostability of the enzyme can easily be tested by heating the enzyme before the assay. Alternatively, the ordinarily-skilled artisan could simply refer to the extensive literature to identify a suitable candidate enzyme for use in the methods of the invention. In either case, one of ordinary skill in the art who sought to make species of the genus of thermostable DNA polymerase enzymes for use in the claimed methods would not synthesize enzymes containing each of the species of critical motif. Rather, the ordinarily skilled artisan would first identify an enzyme that is thermostable and has DNA polymerase activity.

Next, one of ordinary skill in the art would confirm that the enzyme so identified is a thermostable DNA polymerase enzyme by comparing the primary structures of the identified thermostable DNA polymerase to the primary structures of known thermostable DNA polymerase enzymes. The amino acid sequences of numerous thermostable DNA polymerase enzymes are well-known to the art and incorporated by reference into the specification through the '379 patent. *See* the specification at page 3, lines 24-27 and the '379 patent at column 10, line 51 to column 11, line 55. Based upon the known correlation between the primary structure, *e.g.*, the amino acid sequence, and the function, *e.g.*, thermostability and

DNA polymerase activity, of thermostable DNA polymerase enzymes, one of ordinary skill in the art can easily and routinely confirm that a particular enzyme is a thermostable DNA polymerase enzyme.

After identifying a particular thermostable DNA polymerase enzyme, one of skill in the art can then routinely identify the location of the critical motif in any thermostable DNA polymerase using, for example, the claimed sequence (*e.g.*, SEQ ID NO.:1) and alignment algorithms as taught in the specification at page 13, lines 18-28. These algorithms allow one of ordinary skill in the art to identify the particular primary structure, *e.g.*, the critical motif, that permits the use of the thermostable DNA polymerases in the methods of the invention. The ordinarily-skilled artisan can then routinely determine whether the thermostable DNA polymerase enzyme naturally comprises an appropriate residue at position 4 of the critical motif. If the thermostable DNA polymerase enzyme does not naturally comprise the appropriate residue at position 4 of the critical motif, the ordinarily-skilled artisan can routinely construct such a polymerase using, for example, site directed mutagenesis protocols as described in the specification at page 14, lines 23-27. If the thermostable DNA polymerase enzyme naturally comprises an appropriate residue at position 4 of the critical motif, the ordinarily-skilled artisan will recognize that the thermostable DNA polymerase enzyme is suitable for use in the methods of the present invention without further alteration. Thus, one of ordinarily skill in the art can make thermostable DNA polymerases for use in the methods of the invention with no more than routine experimentation.

The foregoing discussion shows that one of skill in the art need not randomly test a large number of different amino acid combinations in the critical motif to determine which thermostable enzyme has DNA polymerization and reverse transcription activity. Rather, one of skill in the art would identify a thermostable DNA polymerase based upon its functional and primary-structural similarity with other such enzymes, then modify the enzyme according to the disclosure of the present application if necessary. Thus, Applicants respectfully submit that the present application fully enables one of skill in the art to practice the entire scope of the claimed methods for reverse transcribing an RNA.

The PTO argues that the claims are not enabled because the amino acid residues comprising the critical motif are not completely conserved, and the effect of changes to the amino acid composition of the critical motif at positions other than position 4 on reverse transcription activity is allegedly unpredictable. Applicants respectfully submit the lack of complete conservation within the critical motif of the thermostable DNA polymerase

enzymes does not affect the ability of one of skill in the art to use the full scope of the claimed methods.

Applicants have described a critical motif of a thermostable DNA polymerase enzyme, wherein the identity of the amino acid at position 4 of the critical motif affects the reverse transcription activity of the enzyme. As described above, one of skill in the art can readily recognize the location of the critical motif within the thermostable DNA polymerase based upon the teaching provided by the specification. The lack of complete conservation does not affect the ability of one of skill in the art to locate the critical motif. Indeed, the present application shows that one of skill in the art is able to identify the critical motif despite the lack of complete conservation by presenting the critical motifs of thermostable DNA polymerase enzymes from 12 different bacterial species. *See* Table 1 at page, 12, lines 1-20. After identifying the critical motif, the ordinarily skilled artisan can easily alter the residue at position 4 of the critical motif, if necessary, for use in the methods of the invention. Accordingly, one of skill in the art is able to practice the full scope of the claimed methods notwithstanding the lack of complete conservation of the critical motif.

Other *Wands* factors also suggest that the specification enables one of ordinary skill in the art to practice the claimed methods without undue experimentation. Indeed, the PTO appears to base the rejection of the claims as not enabled entirely upon the breadth of the claimed invention. Accordingly, Applicants presume that the PTO has correctly determined that each of the other *Wands* factors support the enablement of the rejected claims.

For example, the specification provides examples of construction of and reverse transcription using 19 different thermostable DNA polymerase enzyme mutants derived from *Thermus thermophilus* DNA polymerase, each enzyme comprising a different naturally-occurring amino acid at position four of the critical motif. *See* example 2, pages 19-24. Of these 19 thermostable DNA polymerase enzyme mutants, all but enzymes having A, G, or P at position 4 of the critical motif exhibit increased reverse transcription activity. Thus, the specification provides several working examples showing the construction and use of thermostable DNA polymerase enzymes in the methods of the invention.

The level of ordinary skill of one in the art also suggests that any experimentation necessary to practice the full scope of the invention is routine rather than undue. The applicable arts, including molecular biology, biochemistry, enzymology, *etc.*, are well developed and the techniques for the construction and use of the thermostable DNA polymerase enzymes are well known. Given the disclosure of the present application, one of skill in these arts can routinely construct and use the thermostable DNA polymerase enzymes

in the methods of the present invention as described above. Accordingly, this factor reinforces the conclusion that the specification fully enables one of skill in the art to practice the invention as claimed.

3. *Reverse Transcription Activity does not Depend on Mutations Outside the Critical Motif*

The PTO also argues that the claims might not be enabled because the specification does not provide sufficient guidance as to the effects of additional mutations in a thermostable DNA polymerase enzyme on reverse transcription activity. The additional mutations indicated by the PTO include an F667Y mutation and a G46D mutation. In response, Applicants respectfully submit that the specification provides sufficient teaching for one of skill in the art to assess the effect of such mutations on reverse transcription activity.

To begin with, Applicants are puzzled by the PTO's reference to F667Y and G46D mutants of *Thermus aquaticus* DNA polymerase as Applicants believe that the specification of the present application does not refer to these particular mutants. In addition, Applicants believe that the neither the F667Y mutation nor the G46D mutation would affect the reverse transcription activity of a thermostable DNA polymerase enzyme.

First, Applicants believe that one of skill in the art would not expect the G46D mutation to affect reverse transcription activity because this mutation is in an entirely different structural domain of the thermostable DNA polymerase from the critical motif. The specification teaches at page 18, lines 25-29, that a similar mutation, G46E, attenuates the 5′ nuclease activity of the thermostable DNA polymerase. The structural domain responsible for the 5′ nuclease activity of a thermostable DNA polymerase is different and separate from the structural domain that comprises the critical motif. Therefore, one of skill in the art would not expect the G46D mutation to affect reverse transcription activity.

Moreover, the examples presented in the present application show that a G46E mutation does not affect the reverse transcription activity of the thermostable DNA polymerase enzymes. In particular, Examples 1 and 2 compare the reverse transcription activity of 19 *Tth* mutant thermostable DNA polymerase enzymes, each of which is mutated to an amino acid other than E at position 4 of the critical motif, to that of a *Tth* DNA polymerase enzyme comprising E at position 4 of the critical motif. Both the 19 mutant *Tth* DNA polymerase enzymes and the control *Tth* DNA polymerase enzyme that comprises E at position 4 of the critical motif also comprise the G46E mutation. Thus, the experiments

presented in Examples 1 and 2 show that the reverse transcription activity results from the mutation in the critical motif rather than the G46E mutation.

Applicants also believe that the F667Y mutation does not affect the reverse transcription activity of the thermostable DNA polymerases claimed in the present invention. The '379 patent describes the F667Y mutation as allowing more efficient incorporation of dideoxynucleotides at column 3, lines 46-48. It is not believed to affect reverse transcription activity. In addition, the F667Y mutation in *Taq* DNA polymerase corresponds to a F669Y mutation in *Tth* DNA polymerase. None of the mutants described in the examples of the present application comprise the F669Y mutation, showing that the improved reverse transcription activity of these polymerases is the result of the mutation in the critical motif, not the F669Y mutation.

Finally, the examples of the '379 patent show that reduced discrimination against fluorescein family dye-labeled nucleotides results from the critical motif rather than the F667Y mutation, as none of the DNA polymerases that were used in the experiments described in the examples comprise the F667Y mutation. As stated above, the same structural feature, *i.e.*, the critical motif, that reduces discrimination against fluorescein family dye-labeled nucleotides is believed to also result in improved reverse transcription activity. If the PTO has reason to believe that the F667Y mutation would affect reverse transcription activity, Applicants respectfully request that the PTO provide evidence specifically supporting this reasoning. In the absence of such evidence, Applicants respectfully submit that the PTO must accept Applicants' belief that the reverse transcription activity of the thermostable DNA polymerases depends on the critical motif rather than the F667Y mutation.

Applicants respectfully submit that the foregoing shows that any experimentation required to practice the full scope of the invention as presently claimed is routine rather than undue. Accordingly, Applicants respectfully suggest that the rejection of Claims 1, 8-13, 20-29, 36-41, and 48-52 under 35 U.S.C. § 112, First Paragraph as not enabled by the specification is in error and earnestly request its withdrawal.

B. The Rejection of Claims 5-7, 17-19, 33-35, and 45-47 under 35 U.S.C. § 112, Second Paragraph

Claims 5-7, 17-19, 33-35, and 45-47 stand rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly indefinite. Without agreeing to the propriety of the present rejection, Applicants respectfully submit that the rejection is moot in view of the cancellation of Claims

5-7, 17-19, 33-35, and 45-47. New Claims 53-68 are presented in favor of the cancelled claims and encompass the use of thermostable DNA polymerase enzymes that naturally comprise the critical motif in the methods of the present invention. Applicants respectfully submit that new Claims 53-68 particularly point out and distinctly claim this subject matter and are accordingly not indefinite. Accordingly, Applicants respectfully request that the rejection of Claims 5-7, 17-19, 33-35, and 45-47 be withdrawn.

C. The Rejection of Claims 1-10 and 12 under 35 U.S.C. § 102(b) and (e)

Claims 1-10 and 12 stand rejected as allegedly anticipated under 35 U.S.C. § 102(b) by European Patent No. 0 902 035 ("the '035 patent") and under 35 U.S.C. § 102(e) by the '379 patent. The disclosures of the '035 patent and the '379 patent are substantially identical; both patents claim priority to the same provisional application, U.S. Provisional Patent Application No. 60/058,525. Accordingly, Applicants will treat the subject matter of these two references together. Applicants respectfully traverse the rejection of Claims 1-10 and 12 as anticipated by the '035 patent and the '379 patent on the grounds that these references do not teach each and every element of the rejected claims. Further, Applicants respectfully traverse the rejections based on the absence of a *prima facie* case that one of skill in the art would recognize the '035 and '379 patents as teaching a method for reverse transcribing an RNA.

1. *The Legal Standard*

The standard governing anticipation under 35 U.S.C. § 102 requires strict identity. *See* M.P.E.P. § 2131. Thus, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir., 1990). Anticipation is not shown even when the differences between the claims and the cited reference are allegedly "insubstantial" and any missing elements could be supplied by the knowledge of one skilled in the art. *See Structural Rubber Prod. Co. v. Park Rubber Co.*, 223 U.S.P.Q. 1264 (Fed. Cir., 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253 (Fed. Cir., 1985), the Federal Circuit explained that even if the prior art teaches "substantially the same thing" as the claimed invention, the reference still cannot anticipate the invention. Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

Furthermore, the single cited reference must enable one of skill in the art to practice the claimed invention in order to anticipate the claim under 35 U.S.C. § 102(b). This requirement mandates that "the single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field." *See Elan Pharmaceuticals, Inc. v. Mayo Foundation for Medical Education and Research* 64 U.S.P.Q.2d 1292 (Fed. Cir., 2002) and *Crown Operations International, Ltd. v. Solutia, Inc.* 62 U.S.P.Q.2d 1917 (Fed. Cir., 2002). In other words, "for the *invention* of [the patent at issue] to be *described* in the [allegedly anticipatory reference], pursuant to § 102(b), the [allegedly anticipatory reference] itself must enable someone to practice the invention of [the patent at issue]. *See Reading & Bates Construction Co. v. Baker Energy Resources Corp.* 223 U.S.P.Q. 645 (Fed. Cir., 1984) (emphasis in original). Thus, the cited reference must enable the ordinarily skilled artisan to recognize that each element of the claimed invention is described in the reference. If one of ordinary skill in the art would not recognize that each element of the claim is disclosed by the reference, then it cannot and does not anticipate the claimed invention under 35 U.S.C. § 102(b).

Finally, the PTO bears the burden of presenting a *prima facie* case of anticipation in order to reject a claim under 35 U.S.C. § 102(b). "The initial burden of establishing a *prima facie* basis to deny patentability to a claimed invention rests upon the examiner." *See Ex parte Levy* 17 U.S.P.Q.2d 1461 (Fed. Cir., 1990). Thus, the examiner must present the operative facts sufficient to support a finding of anticipation of a claimed invention by the cited reference. The foregoing paragraphs establish that an allegedly anticipatory reference must describe each element of the invention as claimed sufficiently to allow one of skill in the art to recognize how to practice the invention. If the examiner cannot establish such facts, the rejection of the claims under 35 U.S.C. § 102(b) is improper and must be withdrawn.

2. ***The Claimed Invention***

The invention as presently claimed relates to a method for reverse transcribing an RNA, that comprises providing a reverse transcription reaction mixture comprising said RNA, a primer, a divalent cation, and a thermoactive DNA polymerase. The thermoactive DNA polymerase is characterized in that in is native form, the DNA polymerase comprises an amino acid sequence that is LXXXXXXXXXE. The amino acid identified by X at position 4 of the amino acid sequence is mutated in comparison to said native sequence to an amino acid other than E, A, G, or P, the amino acid identified by X at position 2 of the amino

acid sequence is S or A, and the amino acid identified by X at position 5 of the amino acid sequence is L or I. The reaction mixture is then treated at a temperature sufficient for the thermoactive DNA polymerase to initiate synthesis of an extension product of the primer to provide a product cDNA molecule that is complementary to the RNA.

3. *The '035 and '379 Patents do not Teach or Suggest Each and Every Element of the Claimed Invention*

In support of the rejection of Claims 1-10 and 12 as anticipated by the '035 and '379 patents, the PTO argues that these references disclose every limitation of the claimed invention. In particular, the PTO refers to the specification's definition of the term "DNA synthesis reaction" as referring to methods of producing copies of DNA including, but not limited to, PCR, strand displacement amplification, primer extension, and reverse transcription. The PTO thus argues that the '035 and '379 patents teach every element of the invention as presently claimed and therefore anticipate Claims 1-10 and 12.

Applicants respectfully submit that the PTO has not presented a *prima facie* case that the '035 and '379 patents disclose each and every element of the claimed methods. For example, Claim 1 recites providing a reverse transcription mixture that comprises an RNA, and the PTO has not identified where '035 and '379 patents teach a template RNA. In addition, Claim 1 recites providing a reverse transcription mixture that comprises a divalent cation, and the PTO has not identified where the '035 and '379 patents teach a divalent cation in a reverse transcription reaction. Claim 1 also recites providing a reverse transcription mixture that comprises a primer, and the PTO has not shown that the '035 and '379 patents teach use of a primer to initiate a reverse transcription reaction.

Finally, Claim 1 recites the step of treating the reverse transcription reaction mixture at a temperature sufficient for the thermostable DNA polymerase to initiate synthesis of an extension product of the primer to provide a cDNA molecule complementary to the RNA template. The PTO has not indicated where the '035 and '379 patents teach the treatment of the reverse transcription reaction at a temperature sufficient for the thermostable DNA polymerase to initiate synthesis of an extension product of the primer to provide a product cDNA molecule that is complementary to the template RNA. Thus, there are at least four elements to the method of reverse transcription recited by Claim 1 of the present application that the PTO has not shown to be taught by the '035 and '379 patents.

Accordingly, Applicants respectfully submit that the rejection of Claims 1-10 and 12 as anticipated by the '035 and '379 patents is erroneous and should be withdrawn.

4. *The PTO has not Shown that the Ordinarily Skilled Artisan would Recognize that the '035 and '379 Patents Describe a Method for Reverse Transcribing an RNA*

Furthermore, Applicants respectfully submit that the PTO has not presented a *prima facie* case that the one of skill in the art would recognize that the '035 and '379 patents teach a method for reverse transcribing an RNA in the absence of the detailed disclosure of the present invention. As described above, the PTO bears the burden of presenting a *prima facie* case showing that each and every element of the claimed invention is sufficiently taught by the cited reference for one of skill in the art to recognize how to practice the claimed invention. Thus, the PTO must show that the ordinarily skilled artisan would have recognized that the '035 and '379 patents describe the presently claimed methods of reverse transcribing an RNA. This, the PTO has not shown.

The '035 and '379 patents describe and claim a variety of methods of producing DNA labeled with fluorescein-family dyes. Two such methods include performing a "DNA synthesis reaction" in the presence of a thermostable DNA polymerase that comprises the critical motif. The '035 and '379 patents define the term "DNA synthesis reaction" to encompass several synthetic reactions, including PCR, strand displacement amplification, transcription mediated amplification, primer extension and reverse transcription. These two methods, and the associated definition of the term "DNA synthesis reaction," are the only references to reverse transcription in the '035 and '379 patents. Significantly, the PTO has not shown where the '035 and '379 patents teach that the thermostable DNA polymerase enzymes that comprise a critical motif have improved reverse transcription activity relative to that of native thermostable DNA polymerase enzymes. In fact, the PTO has not identified where the '035 and '379 patents demonstrate that the described thermostable DNA polymerase enzymes have any reverse transcription activity at all.

Applicants respectfully caution that the comprehensive and detailed disclosure of the present application should not supplement the teaching of the '035 and '379 patents. The present application teaches that the amino acid at position 4 of the critical motif affects reverse transcription activity in addition to discrimination against nucleotides labeled with fluorescein-family dyes. The '035 and '379 patents teach that the amino acid at position 4 of the critical motif surprisingly affects discrimination against nucleotides labeled with fluorescein-family dyes, and claim methods of making DNA labeled with fluorescein-family dyes in a DNA synthesis reaction. The '035 and '379 patents also teach that one method of making such labeled DNA is in a reverse transcription reaction. However, the '035 and '379

patents do not specify that the thermostable DNA polymerases described for use in the DNA synthesis reaction have any reverse transcriptase activity in these reactions. The reverse transcription activity could easily be provided by another enzyme, such as MoMuLV reverse transcriptase. Absent identification of some teaching in the '035 and '379 patents that the thermostable DNA polymerase enzymes that comprise the critical motif have appreciable reverse transcription activity, the PTO has not demonstrated that the ordinarily skilled artisan would recognize that the '035 and '379 patents describe a method for reverse transcribing an RNA with a thermostable DNA polymerase that comprises the critical motif.

As demonstrated by the foregoing, the '035 and '379 patents do not describe each and every element of the invention as presently claimed. Further, the PTO has not presented a *prima facie* case that one of skill in the art would recognize that the '035 and '379 patents describe a method for reverse transcribing an RNA as presently claimed. Thus, the '035 and '379 patents cannot anticipate the methods claimed in the present invention. Accordingly, Applicants respectfully submit that the rejection of Claims 1-10 and 12 under 35 U.S.C. § 102(b) and (e) is in error and earnestly request its withdrawal.

D. <u>The Rejection of Claims 11 and 13-52 under 35 U.S.C. § 103(a)</u>

Claims 11 and 13-52 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over the '379 patent or, alternatively, the '035 patent in view of Kawasaki, 1990, "Amplification of RNA," *PCR Protocols* Ch. 3:21-28 ("*Kawasaki*"). As before, Applicants treat the '035 and '379 patents together as their disclosures are identical. Applicants respectfully traverse the rejection on the grounds the PTO has not presented a *prima facie* case for obviousness in that the combined references do not disclose each and every element of the invention as presently claimed and that there is no motivation or suggestion to combine the two references.

1. <u>*The Legal Standard*</u>

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be *prima facie* obvious over the prior art. *See In re Bell*, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention *prima facie* obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made

by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests or relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology,* 51 U.S.P.Q.2d 1386 (Fed.Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

However, the mere fact that the prior art could be modified to produce the claimed invention does not make the modification obvious unless the prior art also suggests the desirability of the modification. *See In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). Rigorous application of the requirement for a showing of such motivation to combine references is the best defense against the subtle but powerful attraction of an impermissible hindsight-based obviousness analysis. *See In re Dembiczak*, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor 's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight." *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside,* 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a *prima facie* case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

2. ***Neither Kawasaki nor the '035 or '379 Patents Teach or Suggest Reverse Transcription with a Thermostable DNA Polymerase Enzyme in the Presence of Magnesium Ions***

The PTO supports the rejection of Claims 11 and 13-52 as obvious over the '035 and '379 patents in view of Kawasaki by relying on essentially the same portions of the '035 and '379 patents as in the rejection of Claims 1-10 and 12 as anticipated. In particular, the PTO refers to the specification's definition of the term "DNA synthesis reaction" as referring to

methods of producing copies of DNA including, but not limited to, PCR, strand displacement amplification, primer extension and reverse transcription. The PTO admits that the '035 and '379 patents do not specifically teach a method of reverse transcription using magnesium, primers, and DNA polymerase. However, the PTO relies upon *Kawasaki* to provide these elements, as well as teaching incubation of the reaction mixture at 23 to 42 degrees. Thus, the PTO argues that the '035 or '379 patent, when combined with *Kawasaki*, teach each and every element of the claimed invention.

Applicants respectfully submit that none of *Kawasaki*, the '035 patent, or the '379 patent teach or suggest the use of magnesium in a method for reverse transcribing an RNA with a thermostable DNA polymerase as recited by, for example, Claims 13-16, 20-24, 27, 28, 41-44, 48-52, 57-60, and 65-68. *Kawasaki* teaches reverse transcription with a mesophillic retroviral reverse transcriptase, MoMuLV reverse transcriptase, in the presence of magnesium. *See Kawasaki* at page 23. However, *Kawasaki* in no way teaches nor suggests reverse transcription using a thermostable DNA polymerase, which is very different, both functionally and structurally, from mesophillic retroviral reverse transcriptases. Thus, *Kawasaki* cannot teach or suggest reverse transcription with a thermostable DNA polymerase in the presence of magnesium.

In fact, Applicants are the first to describe a method for reverse transcribing an RNA with a thermostable DNA polymerase in the presence of magnesium that works with sufficient sensitivity and efficiency to be practical. The first reports of reverse transcription catalyzed by thermostable DNA polymerases in the presence of magnesium show that this activity was inefficient and insensitive. For example, Tse and Forget demonstrate that 4 μg of total RNA is required to generate sufficient PCR product for ethidium bromide-stained gel visualization, using an abundantly expressed mRNA target, *Taq* DNA polymerase, and magnesium ions. *See* Tse and Forget, 1990, *Gene* 88:293-296, attached hereto as reference AF. Thereafter, it was discovered that the sensitivity and efficiency of reverse transcription reactions catalyzed by thermostable DNA polymerases could be improved by substituting manganese ions for magnesium ions.

The literature discloses numerous examples of such methods for reverse transcribing an RNA using thermostable DNA polymerases in the presence of manganese ions. *See, e.g.*, U.S. Patent Nos. 5,310,652, 5,322,770, 5,407,800, 5,641,864, 5,561,058, and 5,693,517, and Myers *et al.*, 1995, "Amplification with RNA: High Temperature Reverse Transcription with *Thermus Thermophilus* DNA Polymerase," *PCR Strategies* Ch. 5:58-68, identified as reference AE of the Information Disclosure Statement filed on July 16, 2001 ("*Myers*").

Nonetheless, such prior art reverse transcription reactions present significant, undesirable features in comparison to the methods of the present invention, which features are undesirable in many applications for reverse transcription methods. For example, subsequent PCR-based amplification of the cDNA product of reverse transcription with thermostable DNA polymerases in the presence of manganese rather than magnesium ions is less sensitive, requires more cycles, and yields PCR products with more misincorporated nucleotides.

Important among these features is the reduced fidelity of manganese-based amplification methods with thermostable DNA polymerases as compared to magnesium-based amplification methods. As noted above, manganese-based amplification methods misincorporate nucleotides into the DNA product at higher rates than magnesium-based reactions. *See*, for example, the specification at page 29, lines 16-18; Beckman *et al.*,1985, *Biochemistry* 24:5810-5817, attached hereto as reference AG; and Leung *et al.*, 1989, *Technique* 1:11–15, attached hereto as reference AH. But as described above, reverse transcription with prior art thermostable DNA polymerases is not sufficiently sensitive and efficient in the presence of magnesium. Thus, prior art methods have focused on methods of improving the fidelity of manganese-based amplification reactions and/or changing the buffer composition between reverse transcription and PCR-based amplification. *See*, for example, *Myers* at 65.

Another important feature of manganese-based reverse transcription methods using thermostable DNA polymerases is the relative instability of RNA in the presence of manganese at high temperature. Divalent metal ion-catalyzed hydrolysis of RNA is increased in the presence of manganese as compared to magnesium. *See*, for example, Brown D.M., 1974, "Chemical reactions of polynucleotides and nucleic acids," in *Basic Principles in Nucleic Acid Chemistry*, Ts'o P. O. P., *ed.*, Academic Press, New York, pp. 43-44, attached hereto as reference AI. Accelerated manganese ion-catalyzed hydrolysis of single stranded RNA at elevated temperatures adversely affects the detection sensitivity of RT-PCR. Thus, the claimed methods permit reverse transcription using thermostable DNA polymerases at higher temperatures than would otherwise be possible.

Applicants are the first to discover methods that allow reverse transcription and PCR amplification with the same enzyme in the same buffer. The methods depend on use of a thermostable DNA polymerase that has useful reverse transcription activity in the presence of magnesium ions. Applicants have discovered thermostable DNA polymerase enzymes that have useful reverse transcription activity in the presence of magnesium rather than manganese. While the prior art focused on methods of improving manganese-based reverse

transcription and amplification methods, Applicants have significantly advanced the art over these prior art methods because of those methods' deficiencies as discussed above. Therefore, the prior art, including *Kawasaki*, the '035 patent, and the '379 patent, does not teach or suggest Applicants' methods for reverse transcribing an RNA with a thermostable DNA polymerase in the presence of magnesium ions as presently claimed

Because *Kawasaki*, the '035 patent, and the '379 patent in no way teach or suggest a method for reverse transcribing an RNA with a thermostable DNA polymerase enzyme in the presence of magnesium ions, Applicants respectfully submit that Claims 13-16, 20-24, 27, 28, 41-44, 48-52, 57-60, and 65-68 are not obvious over the '035 or '379 patents in view of *Kawasaki*. Accordingly, Applicants earnestly request withdrawal of the rejection of Claims 13-16, 20-24, 27, 28, 41-44, and 48-52 as obvious under 35 U.S.C. § 103(a).

3. ***There is No Motivation or Suggestion to Combine the '035 or '379 Patent with Kawasaki***

Finally, the PTO has not presented a *prima facie* case of obviousness because there is no motivation to combine the '035 or '379 patent with *Kawasaki*. The PTO states that "since *Kawasaki* clearly indicates that the source and type of reverse transcriptase does not appear to be critical, the ordinary artisan would have been motivated to substituted the mutant DNA polymerases of [the '035 or '379 patent] because they have demonstrated increased efficiency."

Applicants respectfully submit that only impermissible hindsight based upon the disclosure of the present application indicates that the mutant DNA polymerases described in the '035 and '379 patents have increased reverse transcription activity. In fact, the '035 and '379 patents do not teach that the thermostable DNA polymerases described for use in the claimed methods have improved reverse transcription activity at all. The '035 and '379 patents merely describe and claim methods of producing DNA labeled with fluorescein family dyes. Rather, Applicants' detailed and comprehensive disclosure in the present application has so convinced the PTO of the improved reverse transcription activity demonstrated by the thermostable DNA polymerases of the present invention that the PTO has understandably, but improperly, attributed that teaching to the '035 and '379 patents.

Parenthetically, Applicants note the complete absence of teaching in the '035 and '379 patents of improved reverse transcription activity by thermostable DNA polymerases that comprise a critical motif in the presence of magnesium ions as discussed above. Since the '035 and '379 patents do not teach that the thermostable DNA polymerases that comprise a

critical motif have improved reverse transcription activity in the presence of magnesium ions relative to prior art thermostable DNA polymerases, one of ordinary skill in the art would not use the polymerases in a method for reverse transcribing an RNA in the presence of magnesium as taught by *Kawasaki*. Further, *Kawasaki* teaches reverse transcription with a mesophillic retroviral reverse transcriptase, MoMuLV reverse transcriptase. Methods of using such mesophillic retroviral reverse transcriptases are very different from methods of using thermostable DNA polymerases to reverse transcribe an RNA, as these enzymes comprise important structural and functional differences. Thus, *Kawasaki* also does not provide motivation to combine this reference with either the '035 or '379 patent. Accordingly, there is no motivation to combine *Kawasaki* with the '035 and '379 patents to reject the Claims 13-16, 20-24, 27, 28, 41-44, and 48-52, directed to methods for reverse transcribing an RNA with a thermostable DNA polymerase in the presence of magnesium ions.

Without a teaching in the '035 and '379 patents that the thermostable DNA polymerase enzymes described therein have improved reverse transcription activity, the ordinarily-skilled artisan would not be motivated to use the enzymes in the reverse transcription methods of *Kawasaki*. In addition, neither *Kawasaki* nor the '035 and '379 patents teach or suggest methods of reverse transcribing an RNA with a thermostable DNA polymerase enzymes in the presence of magnesium ions as recited by, for example, Claims 13 and 41. Accordingly, Applicants respectfully submit that the PTO has not established a *prima facie* case of obviousness and the rejection of Claims 11 and 13-52 as obvious under 35 U.S.C. § 103(a) should be withdrawn.

E. The Rejection of Claims 1, 5, 9, 10, and 12 under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 1, 5, 9, 10, and 12 stand rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over Claim 23 of the '379 patent. Applicants respectfully traverse the rejection on the grounds that Claims 1, 5, 9, 10, and 12 are not obvious variations of Claim 23 of the '379 patent.

1. *The Legal Standard*

Under the judicially-created doctrine of obviousness-type double patenting, a claim must be patentably distinct from a claim of an already issued patent. *See General Food Corp. v. Studiengesellshaft Kohle mbH*, 23 U.S.P.Q.2d 1839 (Fed. Cir. 1992). If the claim at issue defines more than an obvious variation of the patented claim, it is patentably distinct and

rejection of the claim as such is improper. *See id.* The claim at issue can be patentably distinct from the patented claim even when the patented claim "'encompasses' or 'embraces' the subject matter defined by the [claim at issue]." *See In re Kaplan*, 229 U.S.PQ. 678, 681 (Fed. Cir., 1986). Indeed, the fact that a patented claim may dominate the claim at issue is "irrelevant." *See id.* at 682. Rather, the PTO must show that the claim at issue is a "mere variation" of the patented claim that "would have been obvious to those of ordinary skill in the relevant art." *See id.* at 683.

2. *Claim 23 of the '379 Patent Recites a Method for Producing Labeled DNA*

Claim 23 of the '379 patent recites a method for making labeled DNA which comprises providing a thermostable DNA polymerase of defined character, providing a nucleotide labeled with a fluorescein family dye, and performing a DNA synthesis reaction. The thermostable DNA polymerase comprises the amino acid sequence LSVXLGXPVKE, whereby X at position 4 is K and X at position 7 is V or I. The term "DNA synthesis reaction" is defined in the specification of the '379 patent to include methods of producing copies of DNA including, but not limited to, PCR, strand displacement amplification, transcription mediated amplification, primer extension, and reverse transcription.

3. *An Ordinarily-Skilled Artisan would not Regard Claims 1, 5, 9, 10, and 12 as Obvious Variations of Claim 23 of the '379 Patent*

Applicants respectfully submit that one of ordinary skill in the art would not recognize Claims 1, 5, 9, 10, and 12 as obvious variations of Claim 23 of the '379 patent. Claim 1, for example, recites a method for reverse transcribing an RNA that comprises providing a reverse transcription reaction mixture comprising the RNA, a primer, a divalent cation, and a mutant thermoactive DNA polymerase, and treating the reaction mixture at a temperature sufficient for the mutant DNA polymerase to initiate synthesis of an extension product of the primer to provide a cDNA molecule complementary to the RNA. The mutant DNA polymerase is characterized in that in is native form the DNA polymerase comprises an amino acid sequence that is SEQ ID NO:1, the amino acid at position 2 of the amino acid sequence is S or A, the amino acid at position 5 of the amino acid sequence is L or I, and the amino acid at position 4 of the amino acid sequence is mutated in comparison to the native sequence to an amino acid other than E, A, G, or P.

To begin with, the methods recited by, for example, Claim 1 of the present application are not obvious variations of Claim 23 of the '379 patent for all of the reasons discussed in

relation to the rejections under §§ 102(b) and (e) and 103(a). Applicants do not reiterate these arguments here but rather respectfully request that the PTO consider them in connection with the present rejection.

In addition, Claim 1 of the present application, for example, is not entirely within the scope of Claim 23 of the '379 patent as asserted by the PTO. For example, Claim 23 of the '379 patent recites the step of providing a thermostable DNA polymerase that "has reduced discrimination against incorporation of nucleotides labeled with fluorescein family dyes." This limitation is not recited by, for example, Claim 1 of the present application.

Claim 23 of the '379 patent also recites the limitation "providing a nucleotide labeled with a fluorescein family dye." Claim 1 of the present application does not recite such a limitation. A method of reverse transcription as recited by Claim 1 does not require and would not be improved by inclusion of a nucleotide labeled with a fluorescein family dye.

Moreover, several limitations recited by Claim 1 of the present application are not recited by Claim 23 of the '379 patent, supporting the conclusion that Claim 23 is outside the scope of Claim 1. For example, Claim 1 of the present application recites providing an RNA, while Claim 23 of the '379 patent does not. Claim 1 of the present application recites providing a primer, while Claim 23 of the '379 patent does not. Claim 1 of the present application recites providing a divalent cation, while Claim 23 of the '379 patent does not. Claim 1 of the present application recites treating the reaction mixture at a temperature sufficient for the mutant DNA polymerase to initiate synthesis of an extension product of the primer to provide a cDNA molecule complementary to the RNA, while Claim 23 of the '379 patent does not. Thus, there are at least four substantial limitations recited by Claim 1 of the present application that do not appear in Claim 23, showing that Claim 23 of the '379 patent is outside the scope of the present application. Therefore, the ordinarily-skilled artisan would not regard Claim 1 of the present application as an obvious variant of Claim 23 of the '379 patent.

Accordingly, Applicants respectfully submit that the rejection of present Claims 1, 5, 9, 10, and 12 as obvious variations of Claim 23 of the '379 application is erroneous and should be withdrawn.

4. ***The Principles Underlying the Judicially Created Doctrine of Obviousness-Type Double Patenting do not Support the Rejection of the Claims of the Present Application***

The principles underlying the judicially created doctrine of obviousness-type double patenting do not support the rejection of Claims 1, 5, 9, 10, and 12 under that doctrine. At its

bottom, obviousness-type double patenting seeks to prevent the unjustified extension of patent term by forbidding the patenting of obvious variations of patented claims. Applicants have discovered that changes to the region of a thermostable DNA polymerase enzyme that allow incorporation of fluorescein family dye-labeled nucleotides unexpectedly result in improved reverse transcription by these enzymes. This substantial new activity for these enzymes had been previously unappreciated. Thus, Applicants have made a *new invention* distinct from the method described and claimed in the '379 patent. Applicants are entitled to a full term of patent protection for this new invention.

In addition, the judicially created doctrine of obviousness-type double patenting should not be used to reject claims when the claims at issue are allegedly obvious variations of a claim of a patent that qualifies as prior art. Under 35 U.S.C. § 101, a patent claim should not be granted when it is identical to an issued claim, even when the issued claim is found in a patent that is not prior art under § 102. *See In re Vogel and Vogel*, 164 U.S.P.Q. 619, 622 (C.C.P.A., 1970) and *In re Longi* 225 U.S.P.Q. 645, 648 (Fed. Cir., 1985). However, § 101 does not prevent the patenting of obvious variations of an issued claim. *See In re Longi* at 648. Therefore, the judiciary promulgated a narrow, non-statutory doctrine of obviousness-type double-patenting by analogy to § 103 of the patent act, which provides a limited basis for rejecting a claim that is an obvious variation of an issued claim of a patent that does not qualify as prior art. *See id.* at 648.

In the present application, Claims 1, 5, 9, 10, and 12 stand rejected as allegedly obvious variants of Claim 23 of the '379 patent. The '379 patent has been cited as prior art under § 102(e) to the present application. In order for the claims of the present application to be patentable, they must comply with the patent laws as established by Congress; they must be novel and non-obvious over the '379 patent, including its claims. The PTO should not rely on the *judicially* created doctrine of obviousness-type double patenting to reject a claim when the claim complies with the *legislatively* created patent laws and the cited claims are found in a prior art patent. *See, e.g.*, M.P.E.P. § 8.04 II.B. The '379 patent was cited as prior art under 35 U.S.C. 102(e), though Applicants' claims are novel and non-obvious over the '379 patent, as shown in the discussion of the rejections under §§ 102(e) and 103(a), above. Therefore, the PTO should not reject Claims 1, 5, 9, 10, and 12 under the limited, non-statutory doctrine of obviousness-type double patenting when these claims comply with each and every requirement of the patent laws as set forth by Congress in relation to the '379 patent.

In view of all of the foregoing, Applicants respectfully submit that the rejection of Claims 1, 5, 9, 10, and 12 under the judicially created doctrine of obviousness-type double patenting is erroneous and earnestly request its withdrawal.

F. The Rejection of Claims 11, 13, 17, 20-29, 33, 36-41, 45, and 48-52 under the Judicially Created Doctrine of Obviousness-type Double Patenting

Claims 11, 13, 17, 20-29, 33, 36-41, 45, and 48-52 stand rejected under the judicially created doctrine of obviousness-type double patenting over Claim 23 of the '379 patent in view of *Kawasaki*. Applicants respectfully traverse the rejection on the grounds that one of ordinary skill in the art would not regard the rejected claims as obvious variations of Claim 23 of the '379 patent, even when supplemented by the disclosure of *Kawasaki*.

Each of the arguments set forth above in relation to the rejection of Claims 1, 5, 9, 10, and 12 under the judicially created doctrine of obviousness-type double patenting apply equally well to the rejection of Claims 11, 13, 17, 20-29, 33, 36-41, 45, and 48-52. Accordingly, Applicants do not repeat them here but rather respectfully request the PTO to consider these arguments in connection with the present rejection.

In addition, Applicants respectfully submit that neither Claim 23 of the '379 patent nor *Kawasaki* teach or suggest methods for reverse transcribing an RNA with a thermostable DNA polymerase in the presence of magnesium. Claims 13, 17, 20-24, 27-28, 41, 45, and 48-52 each recite providing, among other elements, magnesium and a thermostable DNA polymerase. As described above, Applicants have discovered a method for reverse transcribing an RNA that provides all of the advantages of methods that use a thermostable DNA polymerase and magnesium in a single reaction. One of skill in the art would not and could not recognize these methods based upon the disclosure of Claim 23 combined with *Kawasaki*. Thus, Claims 13, 17, 20-24, 27-28, 41, 45, and 48-52 are not mere obvious variants of Claim 23 of the '379 patent even when considered in relation to *Kawasaki*.

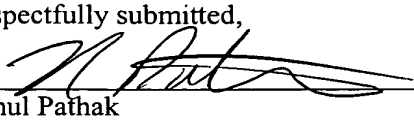
In view of the foregoing, Applicants respectfully submit that the rejection of Claims , 13, 17, 20-29, 33, 36-41, 45, and 48-52 under the doctrine of obviousness-type double patenting is in error and should be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. The PTO is invited to telephone the undersigned attorney at (650) 849-7607, if a teleconference would facilitate passage of the claims to issuance.

Respectfully submitted,

Date: June 30, 2003



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